IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AVENTIS PHARMA S.A., SANOFI-AVENTIS U.S., LLC, Plaintiffs,	)	C.A. No. 07-721-GMS (Consolidated)
v.	)	**REDACTED PUBLIC VERSION**
HOSPIRA, INC, APOTEX, INC. and APOTEX CORP., Defendants.	)	

CORRECTED VERSION:
PLAINTIFFS' POST-TRIAL PROPOSED
FINDINGS OF FACT AND CONCLUSIONS OF LAW

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Explanation of Citation Forms

- "'512 patent" refers to U.S. Patent No. 5,714,512 B1 (the "'512 patent"), which is Joint Trial Exhibit 1.
- "'561 patent" refers to U.S. Patent No. 5,750,561 B1 (the "'561 patent"), which is Joint Trial Exhibit 3.
- "Apotex" refers collectively to Apotex, Inc. and Apotex Corp., two of the defendants in this action. (UF ¶¶ 6-7.)
- "ATX ___" refers to an Apotex trial exhibit in this action.
- "FDA" refers to the United States Food and Drug Administration.
- "Hospira" refers to either Hospira, Inc., a defendant in this action, or its predecessor Mayne Pharma. (*See* UF ¶ 5.)
- "HTX __" refers to a Hospira trial exhibit in this action.
- "JTX __" refers to a Joint trial exhibit in this action.
- "NCI" refers to the National Cancer Institute.
- "*Orange Book*" refers to the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluation*.
- "Patents-in-Suit" refer collectively to the '512 and '561 patents.
- "PTX __" refers to a Plaintiffs trial exhibit in this action.
- "Rhône Poulenc" or "Rhône-Poulenc Rorer" refers to a corporate predecessor of Plaintiffs.
- "sanofi-aventis" or "Plaintiffs" refer collectively to Aventis Pharma S.A. and sanofi-aventis U.S., LLC, the two plaintiffs in this action. (UF ¶¶ 1-2.)
- "UF ¶ ___" refers to paragraphs of the Parties' Statement of Uncontested Facts, filed on September 21, 2009 (D.I. 314, Appendix A).

I. BACKGROUND OF THE INVENTION

1. This Hatch-Waxman patent infringement case relates to the development of a new formulation for the class of cancer drugs known as the taxanes. The named inventors here succeeded where leading researchers for years had failed: formulating taxanes without using the toxic excipient Cremophor. They did so by developing a polysorbate-based formulation, (*see, e.g.*, '561 patent (JTX 3) at 2:25-30), an excipient that had been considered and rejected in the art (*see infra* ¶ 3). Their innovation, embodied in the drug product Taxotere,[1] allows the taxane "docetaxel" to be administered to patients without the life-threatening anaphylaxis associated with the prior Cremophor-based formulation.

2. Taxanes are a class of compounds that have an almost miraculous ability to kill cancer cells. (*See* UF ¶¶ 10-13.) However, they are also virtually insoluble in water and thus notoriously difficult to formulate for intravenous administration to patients. ('512 patent (JTX 1) at 2:8-11; Tr. 389:21-390:3, 392:23-395:16 (Fabre).) Because taxanes are so cytotoxic, they must be administered intravenously as very dilute, aqueous solutions known as "perfusions." But taxanes' extreme water insolubility means that they will have a strong tendency to precipitate out of the perfusion, preventing administration of the drug and, when precipitation occurs in the patient's bloodstream, potentially leading to life-threatening complications. As a result, the formulator's task is to find excipients that are able to keep the taxane in solution long enough to allow the drug to be administered to patients in a way that is safe and effective, (Tr. 392:23-395:16 (Fabre); 811:8-812:17 (Liu)), and that do not interfere with the safety and effectiveness of the formulation (*see* Tr. 1271:21-1272:12 (Williams)).

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[1] The ® symbol for Taxotere, a registered trademark of sanofi-aventis, will be omitted herein.

3. The first taxane to be developed was paclitaxel (also known as "taxol"). While its antitumor potential was recognized in the 1960s, clinical development was delayed by difficulties in synthesizing and formulating. (*See* JTX 15 at 1247.) A wide variety of excipients, including polysorbate, were tried and rejected before a suitable formulation was discovered. (Tr. 1267:24-1268:21 (Williams); Tr. 1476:14-1477:2 (Park); PTX 209 at 135.) The formulation selected was a 50-50 mixture of ethanol and the surfactant Cremophor. Phase I clinical trials using this formulation began in late 1983. (Tr. 111:19-21 (Burris).)

4. Unfortunately, these Phase I trials were a failure. Patients administered the formulation suffered an unacceptably high rate of anaphylaxis. (Tr. 111:19-112:19 (Burris).) Anaphylaxis (also called "anaphylactic shock", Tr. 953:19-954:10 (Myrdal)) is among the most serious adverse reactions associated with cancer chemotherapy: it is a severe and life-threatening allergic reaction whose hallmark is rapid deterioration of the cardiovascular system to the point of vascular or circulatory collapse. (Tr. 112:20-113:13 (Burris); 1093:9-16 (Childs); 1389:25-1390:25 (Handy).) The high incidence of anaphylaxis stopped the Phase I trials and "threatened the prospects of taxol's further development." (JTX 15 at 1251.)

5. The anaphylaxis was widely blamed on the Cremophor used in the formulation. (Tr. 122:5-13 (Burris).) As a result, researchers attempted to find a new formulation for paclitaxel that avoided Cremophor but did not precipitate when diluted to a perfusion. (PTX 413 at 170; *see also* Tr. 934:22-935:11 (Myrdal).) Efforts to find a Cremophor-free taxane formulation began in the mid-1980s, shortly after the problems with anaphylaxis first arose with the Taxol formulation. (Tr. 943:7-944:25 (Myrdal); *see, e.g.*, JTX 92.) Until Plaintiffs' breakthrough, however, none of these efforts succeeded. (Tr. 938:16-939:6 (Myrdal); *see also* Tr. 125:17-25 (Burris).) A 1990 publication by many of the leading scientists involved with paclitaxel

concluded bluntly that "[a]t present, there is no suitable substitute for Cremophor EL in taxol formulation." (JTX 145 at 1267; *see also* Tr. 246:14-247:25 (Burris).)

6. The sanofi-aventis scientists named as inventors on the Patents-in-Suit specifically set out to find a Cremophor-free taxane formulation in order to avoid anaphylaxis. (Tr. 388:16-389:20 (Fabre).) Though docetaxel had been developed by sanofi-aventis in 1986, the compound had previously been formulated, like paclitaxel, in a 50-50 mixture of ethanol and the surfactant Emulphor. (Tr. 836:8-17 (Myrdal); JTX 9 at 10:5-8.)[2] To find a Cremophor-free formulation, sanofi-aventis scientists literally went back to the drawing board, investigating not merely a wide variety of possible excipients available to a formulator at the time, but also a wide variety of formulation *approaches*—micellar solutions, emulsions, microemulsions, mixed-micelles, and solvent/cosolvent approaches. (Tr. 398:15-404:9 (Fabre); JTX 60-T at SA00885060.) After numerous failures, the inventors decided to proceed with a formulation using the surfactant polysorbate 80, based on preliminary tests suggesting that a 50-50 mixture of ethanol and polysorbate 80 might be able to achieve the necessary physical stability in a perfusion.

7. However, there remained grave concerns about pursuing a polysorbate-based taxane formulation. The published literature raised serious concerns about the toxicity of polysorbate in a perfusion, particularly in the unprecedented amounts necessary to formulate highly insoluble taxanes like paclitaxel and docetaxel. Not only was it unclear whether such high concentrations of polysorbate could be safely administered to patients in light of that surfactant's known adverse effects on cardiac function, (Tr. 1326:12-1328:10, 1329:15-1330:17 (Rodricks)), but additional literature suggested that polysorbate was also associated with the same problem of anaphylaxis

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[2] As Defendants' expert acknowledged, Emulphor is simply another brand name for the same polyethoxylated castor oil surfactant as Cremophor. (Tr. 837:4-8 (Myrdal).)

as Cremophor (Tr. 407:1-10 (Fabre); JTX 161 at SA00879677).

8. At the time of the invention, polysorbate was not typically used in perfusions. (Tr. 405:11-14 (Fabre); 919:13-920:10 (Myrdal); 1473:7-23 (Park).) Even where polysorbate was used in formulating a drug substance into a subcutaneous or intramuscular injection, Cremophor was instead used to formulate the drug substance in a perfusion (*i.e.*, intravenous infusion). (Tr. 917:10-17 (Myrdal); 1473:7-23, 1486:10-20 (Park).) And a then-recent attempt to use polysorbate 80 in the intravenous vitamin supplement E-Ferol had ended in disaster, with the death of scores of premature infants. (Tr. 1330:18-1332:4 (Rodricks).)

9. The sole precedent for using polysorbate in formulating cancer drugs in perfusions was etoposide. (Tr. 919:13-920:10 (Myrdal).) But the etoposide formulation is quite different from that used for docetaxel, which requires many times more polysorbate than etoposide to achieve a stable perfusion, (Tr. 920:24-921:5 (Myrdal)), and the etoposide formulation includes cosolvents like benzyl alcohol that are unsuitable for taxanes. (Tr. 794:9-795:1 (Liu); 920:24-921:5, 922:17-923:18 (Myrdal); *see also* Tr. 1467:4-1469:8 (Park).)

10. To determine whether a polysorbate-based formulation of docetaxel could safely be administered to humans, the inventors decided in 1989 to conduct animal toxicology tests on the formulation. (Tr. 412:20-25 (Fabre).) At the same time, because of concerns regarding the suitability of polysorbate for use in intravenous infusions, the company insisted that the inventors also pursue a docetaxel formulation without polysorbate. (Tr. 411:12-23 (Fabre).)

11. The toxicity of the proposed polysorbate 80 formulation was tested using the standard protocols for animal toxicology testing published by the NCI. (Tr. 1320:10-1324:4 (Rodricks).) The results were extremely discouraging. (Tr. 414:4-9 (Fabre).) In particular, the toxicology testing estimated that the highest non-lethal dose of the formulation (the predicted maximum

tolerated dose in humans) was well *below* the dose necessary for therapeutic activity. (Tr. 414:24-416:7 (Fabre).) Based on these results, many in the company believed that the attempt to develop a taxane formulation with polysorbate should be abandoned and docetaxel instead formulated in Cremophor, like paclitaxel had been. (Tr. 417:5-14 (Fabre).)

12. As a result, in 1990 the inventors pursued alternative formulations, such as a perfusion based on an "intralipid" emulsion. None of these alternatives, however, were able to keep docetaxel in solution long enough to be suitable as a perfusion. (Tr. 423:6-15 (Fabre); JTX 60-T at SA00885079-80.) The inventors also tried formulations analogous to the etoposide formulation—that is, with greatly reduced polysorbate 80 concentrations and the addition of cosolvents such as benzyl alcohol—in the hope that reducing the polysorbate 80 would reduce the toxicity believed to be associated with it. (Tr. 418:17-419:4, 420:6-11 (Fabre).) Here, too, the alternatives failed because the docetaxel was too hard to keep in solution. None of the "etoposide-type" docetaxel formulations had sufficient physical stability to serve as perfusions. (Tr. 420:12-423:5 (Fabre); JTX 60-T at SA00885060, 5073-75.) Based on this testing, the inventors concluded that alternatives such as an etoposide-type formulation did not work and that the only way to formulate taxanes without Cremophor was to use high concentrations of polysorbate, despite the risks of toxicity and anaphylactic shock raised by the published literature and the toxicology testing. (Tr. 492:6-498:19 (Fabre); JTX 60-T at SA00885076-78.)

13. The initial Phase I clinical trials went forward with the polysorbate 80-based formulation in June 1990. (*See* Tr. 424:18-425:8 (Fabre).) Because of the discouraging toxicology, onerous precautions were imposed on the trials. For example, a greater than customary number of different clinical sites were used, following different administration regimens, in anticipation of anaphylactic events. (Tr. 417:19-418:7 (Fabre).) In addition, the starting dose for Phase I was set

at 5 mg/m^2, far below the 100 mg/m^2 thought necessary for effectiveness, because of toxicity concerns. (Tr. 418:8-16 (Fabre).)

14. The bad toxicology meant that development of the formulation would be long and challenging, and many in the company did not expect to succeed. (Tr. 416:8-417:14 (Fabre).) However, the Phase I trials defied the predictions of the NCI toxicology testing. Following a program of slow dose escalation, the Phase I clinical trials were able to demonstrate that the polysorbate 80-based formulation was tolerable above 100 mg/m^2 and showed activity at that level. (Tr. 427:1-429:23 (Fabre).) At the same time, no anaphylaxis was observed in any of the Phase I clinical trials. (Tr. 429:24-430:3 (Fabre).) This was true even though no premedication had been used during those trials. (Tr. 141:14-145:3 (Burris).) In stark contrast to the experience with the Cremophor-based Taxol formulation, (Tr. 111:19-112:19 (Burris)), here it had not been necessary either to slow the infusion rate nor premedicate; there was no anaphylaxis with Taxotere when administered in one hour without premedication. (Tr. 124:6-23, 144:9-147:1 (Burris); 1119:10-22 (Childs).) Five days after the inventors received word of these Phase I results, they filed their patent application. (Tr. 430:4-10 (Fabre).)

15. One other unexpected discovery had occurred during this time. In the course of attempting to retrieve docetaxel from an existing polysorbate 80/ethanol stock solution by evaporating the ethanol, the inventors discovered that the ethanol was actually unnecessary to keep the docetaxel in polysorbate 80. (Tr. 423:16-424:9 (Fabre).) This was surprising because the taxanes were believed to be insoluble in pure surfactant (hence the use of large amounts of ethanol in Taxol); a misimpression now understood to result from the fact that the taxanes dissolve very slowly in pure surfactant, which makes them appear insoluble in routine solubility studies. (*See* Tr. 656:21-658:4 (Myerson).) This further discovery gave rise to a polysorbate-

based docetaxel formulation without ethanol. (Tr. 423:16-424:17 (Fabre).)

16. Throughout the clinical trials, the incidence of anaphylaxis remained extremely low—well under 1%. (*See* Tr. 179:9-14 (Burris); JTX 69 at SA0091577 (Phase I), SA00091624 (Phase II).) Sanofi-aventis gained FDA approval for its polysorbate 80-based docetaxel formulation, under the name Taxotere, on May 14, 1996, in NDA No. 20-449. (UF ¶¶ 17, 19.)

17. The inventors' patent application entered the United States as two separate PCT applications on July 3, 1992. The '512 patent issued on February 3, 1998; and the '561 patent on May 12, 1998. (UF ¶¶ 14, 15.) Both patents were initially assigned to Rhône-Poulenc Rorer (a corporate predecessor of both Plaintiffs), are currently owned by Aventis Pharma S.A., are listed in the *Orange Book* (UF ¶ 18), and are both set to expire on July 3, 2012.

18. The same five claims are asserted against both defendants: Claims 2, 5 and 10 of the '561 patent and Claims 7 and 33 of the '512 patent. (UF ¶¶ 47-48.)

II. CLAIM 5 OF THE '561 PATENT IS INFRINGED AND NOT INVALID

19. Claim 5 of the '561 patent reads:

> 5. A perfusion, which contains approximately 1 mg/ml or less of compound of formula as defined in claim 1, and which contains less than 35 ml/l of ethanol and less than 35 ml/l of polysorbate, wherein said perfusion is capable of being injected without anaphylactic or alcohol intoxication manifestations being associated therewith.

20. The Court has construed the term "which contains" to mean "comprising." (D.I. 347.)

21. The Court has construed the term "capable of being injected without anaphylactic or alcohol intoxication manifestations" to mean "having a reasonable expectation of being injected without causing anaphylactic or alcohol intoxication manifestations." (*Id.*)

A. Construction of "Perfusion"

22. The parties previously agreed that the term "perfusion" means "a solution suitable for infusion into patients including at least active pharmaceutical ingredient and an aqueous infusion

fluid such as physiological saline or glucose." (D.I. 44 at 3.) At the Pretrial Conference, it became apparent that the parties did not have a common understanding as to what it meant to be "suitable for infusion into patients," and accordingly, the Court indicated that it would construe "perfusion" following trial. (D.I. 345 at 66:5-10.)

23. The parties agree that the term "perfusion" refers at least to a dilute aqueous solution for intravenous infusion administered to patients through an IV bag. (Tr. 168:9-169:19 (Burris); 1031:24-1032:4 (Calvert).) The dispute is whether, to be a perfusion within the meaning of the claims, the solution must also be (1) physically stable (that is, without precipitation) for at least eight hours; and (2) safe and effective for administration to patients.

1. The Perfusions of the Claim Must Be Physically Stable for at Least Eight Hours

24. Construction of a disputed claim term focuses primarily upon the intrinsic evidence: the claim language itself, the specification of the patent, and its prosecution history. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1316-17 (Fed. Cir. 2005) (*en banc*); *Medrad, Inc. v. MRI Devices Corp.*, 401 F.3d 1313, 1319 (Fed. Cir. 2005) ("We cannot look at the ordinary meaning of the term ... in a vacuum. Rather, we must look at the ordinary meaning in the context of the written description and the prosecution history." (internal quotation omitted)).

25. The intrinsic evidence establishes that adequate physical stability (specifically, eight hours) is an attribute of the claimed perfusion. This is stated expressly in the specification: "The new perfusions are stable from a physical standpoint, that is to say no precipitation phenomenon is seen to appear within approximately 8 hours." (JTX 3 at 2:43-45.) The patent reports the physical stability for every perfusion described in the patent, demonstrating that greater than eight hours (often twenty-one hours or more) of physical stability was achieved in each case. (JTX 3 at 2:66-67; 3:14-15; 3:24-26 & tbl.1.) Such statements alone establish that the claimed

perfusion must have the requisite physical stability of eight hours or more. *See Microsoft Corp. v. Multi-Tech Sys., Inc.*, 357 F.3d 1340, 1351-52 (Fed. Cir. 2004) (construing the term "multiplexing" to include requirement of "prioritization of voice data over computer data" because the specification taught that this prioritization is "central to the functioning of the claimed inventions"); *AstraZeneca AB v. Mutual Pharm. Co.*, 384 F.3d 1333, 1339 (Fed. Cir. 2004) (statements limiting claim scope need not be expressed in rigid definitional format, limiting term "solubilizer" to surfactants based on statements in specification describing the advantages of surfactants, the disadvantages of other types of solubilizers, and the fact that the examples provided in the patent were all surfactants).

26. Any doubt about whether the claim is limited to intravenous infusions with at least eight hours physical stability is resolved by the prosecution history. During prosecution, Applicants expressly distinguished prior art (specifically, the Tarr article, JTX 16) from the claimed invention on the basis that the perfusions described in Tarr did not have sufficient physical stability. (JTX 4 at SA00013133-34 ("Applicants have carried out test[s] to show that dilutions of Tarr's disclosed composition with glucose serum to prepare injectable solutions are simply not stable long enough to be useful in making perfusions.").) Indeed, Defendants' expert conceded that the distinction between Claim 5 and Tarr made during prosecution was Tarr's lack of eight hours of physical stability. (Tr. 1236:21-1237:10, 1238:9-1239:10 (Williams).) It is a fundamental principle of claim construction that arguments made during prosecution to distinguish the prior art serve to limit construction of the claim. *See, e.g., Seachange Int'l, Inc. v. C-Cor., Inc.*, 413 F.3d 1361, 1372-73 (Fed. Cir. 2005) (relying on arguments made to distinguish prior art in construing the term "network" to require the network of the claims to include "point to point interconnections"); *Lampi Corp. v. Am. Power Prods. Inc.*, 228 F.3d 1365, 1374 (Fed.

Cir. 2000) ("[B]y distinguishing the claimed invention over the prior art, an applicant is indicating what the claims do not cover." (internal quotation omitted)).

27. Construing the claimed perfusions to require eight hours' physical stability also comports with the extrinsic evidence. Both sides' formulators agreed that a major challenge in formulating taxane perfusions is that taxanes' extreme water insolubility make them highly prone to precipitating out. (Tr. 392:23-394:4 (Fabre); Tr. 811:8-21 (Liu).) As a result, a major concern of formulators is to achieve adequate physical stability. (Tr. 394:5-19 (Fabre); 812:7-17 (Liu).) The eight-hour minimum expressly stated in the patent, (JTX 3 at 2:43-45), is consistent with the common-sense standard, to which Defendants' witnesses agreed, that a safety margin is necessary because precipitation may occur more readily in the clinic than the laboratory. Accordingly, an eight-hour minimum ensures at least four hours' stability for preparation and administration in the hospital setting. (Tr. 803:9-18 (Liu); 1237:11-23 (Williams); *see also* Tr. 421:19-422:10 (Fabre) (an eight-hour minimum was desirable because nurses could mix the perfusion and administer it during their shift, ensuring that the product was used properly).)

28. The prior art similarly reflects this concern with the physical stability. For example, the Tarr article describes as a "major problem" precipitation of drug upon dilution into a perfusion or administration into the blood stream. (JTX 16 at 31; *see also* Tr. 1244:11-23 (Williams).) And Tarr specifically reports that the perfusions attempted there, paclitaxel with ethanol and the two surfactants pluronic L64 and polysorbate 80 were *not suitable* for administration through an IV bag system (that is, as a perfusion) because they lacked sufficient physical stability. (JTX 16 at 32; Tr. 1241:9-13 (Williams).) Thus, construing the claimed perfusions to require a minimum of eight hours' physical stability accords with the principle that patent claims are understood in light of the problem to be solved. *See, e.g., CVI/Beta Ventures, Inc. v. Tura LP*, 112 F.3d 1146,

1160 (Fed. Cir. 1997) ("In construing claims, the problem the inventor was attempting to solve, as discerned from the specification and the prosecution history, is a relevant consideration.")

2. The Perfusions of the Claim Must Be Safe and Effective

29. The term "perfusion" is also properly construed to be limited to solutions that are *safe* and *effective* for intravenous infusion. Defendants do not dispute that the term "perfusion" is limited to pharmaceutical compositions—that is, to solutions intended for administration to patients. As Defendants' Dr. Williams conceded, a perfusion that was not safe and effective would have no utility. (Tr. 1234:12-16; 1235:16-1236:2.) For this reason, based on the understanding that claims should be construed to be operable and suitable for their intended use, claims to pharmaceutical compositions, particularly those intended for intravenous administration, are limited to compositions suitable for such administration—that is, compositions that are safe and effective. *See, e.g., Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 579 F. Supp. 2d 199, 205 (D. Mass. 2008) (construing "pharmaceutical composition" to mean "suitable for administration to humans" and finding prior art to be suitable for administration because it was "without any evidence of pyrogens or any significant deleterious consequences" and animal testing had shown no "adverse effects"); *Pharmacia & Upjohn Co. v. Sicor Inc.*, 447 F. Supp. 2d 363, 370 (D. Del. 2006) (construing "physiologically suitable" in the context of an injectable formulation to mean "sterile, pyrogen-free, and otherwise suitable for administration to humans").[3] *see also Purdue Pharma, LP v. F.H. Faulding & Co.*, 48 F. Supp. 2d 420, 437 (D. Del. 1999) ("'[E]ffective treatment of pain' means that an individual patient is provided with adequate pain relief . . . without unacceptable side effects.").

[3] In *Pharmacia*, the court did not impose a stability limitation because there was no discussion of stability in the patent or prosecution history. By contrast, stability is repeatedly emphasized in the patent and prosecution history here. (*See, e.g.*, JTX 3 at 2:43-45, 3:14-15.)

30. The requirement of safety and effectiveness is supported by the intrinsic evidence. The specification emphasizes the therapeutic nature of the claimed formulations, (*e.g.*, JTX 3 at 1:31-34), and reports, as an advantage of the invention, the avoidance of toxicity when used "in the clinical situation" (*id.* at 2:25-30). The specification describes the claimed perfusions as advantageous over the prior art Cremophor-based ones specifically with regard to safety and tolerability, (*id.* at 2:25-30, 48-51), a point conceded by Defendants' formulation expert. (Tr. 1253:11-17 (Williams).) Construing the claimed perfusions to include unsafe or intolerable ones would negate the very benefits asserted for the invention in the patent itself. *See Computer Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1378-79 (Fed. Cir. 2008) (construing patent term narrowly based on specification's description of the advantages of the invention).

31. The centrality of safety and effectiveness in formulating perfusions was confirmed by the parties' witnesses. Plaintiffs' expert formulator, Dr. Park, explained that a formulator always considers safety and effectiveness when developing a formulation for clinical use. (Tr. 1438:14-1440:7, 1491:1-1492:11.) Defendants' formulation expert Dr. Williams agreed, stating that the purpose of formulation is "to prepare pharmaceutic agents in a form that are stable and can be administered and tolerated by patients." (Tr. 1251:6-16.) In keeping with this view, Hospira's docetaxel formulator Julie Liu testified that she was attempting to develop a formulation that had sufficient physical stability for human administration, and that was safe and effective. (Tr. 812:3-10.) Defendants' formulation expert Dr. Myrdal stated that prior art taxane formulations that were too toxic for clinical administration were considered failures. (Tr. 937:1-938:3.)

32. Not only were safety and effectiveness central concepts of cancer drug formulation at the time of invention, but they had a well-defined meaning: that the maximum tolerated dose for the formulation was above the minimum effective dose. (Tr. 1312:20-1313:14 (Rodricks).)

B. Both Defendants Infringe Claim 5

33. Where the act of infringement is the filing of a B2 application, the infringement analysis is hypothetical, comparing the asserted claims against the product that is likely to be sold should the FDA approve the application. *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1248-49 (Fed. Cir. 2000). In Hatch-Waxman cases, "[s]tatements in a package insert that encourage infringing use of a drug product are alone sufficient to establish intent to encourage direct infringement" for purposes of inducement to infringe under 35 U.S.C. § 271(b). *Abraxis Bioscience, Inc. v. Navinta, LLC*, 640 F. Supp. 2d 553, 570-71 (D.N.J. 2009); *see also 3M Co. v. Chemque, Inc.*, 303 F.3d 1294, 1305 (Fed. Cir. 2002) (defendant who is aware of a patent and supplies a product to a customer with instructions for use, which when followed lead to infringement, has encouraged acts constituting direct infringement). For liability for "contributory infringement", under 35 U.S.C. § 271(c), "in addition to proving an act of direct infringement, plaintiff must show that defendant knew that the combination for which its components were especially made was both patented and infringing, and that defendant's components have no substantial non-infringing uses." *Lucent Techs., Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1320 (Fed. Cir. 2009) (internal quotation and citation omitted).

34. Both Defendants have filed B2 applications with FDA seeking approval to market generic docetaxel intravenous infusion products. (*See* UF ¶¶ 53, 58.)

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REDACTED

35. Both Defendants' perfusions fall within Claim 5. This was conceded with regard to Apotex's product by Defendants' expert, Dr. Williams, who concluded that "Apotex's perfusion product, when prepared by a pharmacist according to the directions on the label," will meet the compositional limits of the claim, (Tr. 1255:20-1256:9), and that "Apotex's perfusion will be capable of being administered without anaphylactic or alcohol intoxication manifestations being associated therewith", (Tr. 1256:10-17), the final element Claim 5. While Dr. Williams did not separately analyze Hospira's perfusion, there is no dispute that that perfusion too meets the compositional limits of the claim, (JTX 313 at Hospira0049282), and, having precisely the same labeling as the Apotex (and Taxotere) products concerning adverse effects, is "capable of being administered without anaphylactic or alcohol intoxication manifestations being associated therewith." Accordingly, Dr. Williams' analysis makes clear that both Defendants' perfusions meet each and every limitation of Claim 5 of the '561 patent. This conclusion can be confirmed by an element-by-element analysis of the perfusions.

1. "Perfusion"

36. Both the Apotex and Hospira products meet the claim limitation of being a "perfusion." As part of their B2 Applications, both Defendants presented evidence that their respective perfusions were safe and effective for the labeled use, *i.e.*, that perfusions made in accordance with the prescribing information were safe and effective. (*See* JTX 37 at Hospira0049158-61; PTX 116 at API-DOC-0000303.)

37. In addition, both products (and Taxotere) are labeled for a physical stability of four hours. (JTX 70 § 2.10 (Taxotere); JTX 37 at Hospira0049062; PTX 701 § 2.10.) It is well understood in the art that a "safety margin" is built into the four hours on the prescribing information, and that actual stability would be at least eight hours. (Tr. 637:24-638:8 (Kaler); 692:12-693:18 (Myerson); 1237:11-23 (Williams).) Hospira's formulator Julie Liu confirmed that the prescribing information incorporates this safety margin, (Tr. 803:15-18), and that in fact the products have at least eight hours of physical stability—and, indeed, are labeled as such elsewhere (Tr. 803:19-805:6; 806:15-22). Consequently, both the Hospira and Apotex perfusions are safe and effective and meet the requisite minimum physical stability; they thus both comprise "perfusions" within the meaning of Claim 5.

2. Compositional Limits

38. Claim 5 requires the claimed perfusion to contain approximately 1 mg/ml or less of [docetaxel] and less than 35 ml/L of ethanol and polysorbate.

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3. "Capable of Being Injected Without Anaphylactic or Alcohol Intoxication Manifestations Being Associated Therewith"

39. This term means "having *reasonable expectation* of being injected without causing anaphylactic or alcohol intoxication manifestation." (D.I. 347 at 3 (emphasis added).)

40. The alcohol content of both Defendants' perfusions is sufficiently low to provide a reasonable expectation of administering the perfusions without alcohol intoxication manifestations, as explained by Plaintiffs' expert Dr. Burris. (Tr. 180:6-24.) None of Defendants' experts contradicted this testimony, and indeed Dr. Williams agreed with Dr. Burris. (*See* Tr. 1256:10-17).

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, This very low level of anaphylaxis meets the requirement that the products have a reasonable expectation of being injected without anaphylactic manifestations. (Tr. 176:8-178:5 (Burris).)

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42. The reasonable expectation of administering Defendants' perfusions without anaphylaxis is also supported by more than a decade of experience with Taxotere.

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[5] The incidence of anaphylaxis with Taxotere, and thus with the accused products, is extremely low. During the Phase I trials, not one case of anaphylaxis was reported when Taxotere was administered to over 250 patients without premedication. (Tr. 1035:13-18, 1036:24-1037:12 (Calvert).) The overall incidence of anaphylaxis (without regard to premedication) was 0.6%. (Tr. 145:6-147:1 (Burris); *see also* JTX 69 at SA00091577, SA00091675.)

43. Experience since Taxotere approval has confirmed that the incidence of anaphylaxis with Taxotere is extremely rare. Dr. Barry Childs, who as sanofi-aventis' Medical Director for Taxotere is responsible for the post-marketing surveillance of the safety of the product, estimated that out of roughly 300,000 patients treated in the last seven years, there have been *less than ten* reported cases of anaphylaxis. (Tr. 1117:10-1118:10.) Similarly, Nurse Handy, an oncological nurse responsible for the actual administration of Taxotere, has never seen a case of anaphylaxis in the thousands of times she has administered, or supervised the administration of, the drug. (1388:11-15, 1391:1-6.) Both Dr. Childs and Nurse Handy confirmed that, based on their long experience with the drug, Taxotere can be administered with a reasonable expectation of avoiding anaphylaxis. (Tr. 1118:11-24 (Childs); Tr. 1404:21-1405:1 (Handy).)

44. Defendants' expert Dr. Williams conceded that Apotex's perfusion (and thus Hospira's)

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met the claim limitation that the perfusion be "capable of being injected without anaphylactic manifestations being associated therewith." (Tr. 1256:10-17.) Dr. Williams attempted to limit his testimony to administration of the perfusions with premedication. (*Id.*) However, the influence of premedication on the incidence of anaphylaxis was examined during the clinical trials, and premedication was shown *not* to reduce the incidence of anaphylaxis. (Tr. 244:9-245:10 (Burris); JTX 69 at SA00091770 ("No positive impact [of premedication] was found on the incidence of AHSR [acute hypersensitivity reactions (of which anaphylaxis is the most severe type)] . . ."); *see also id.* at SA00091632 (reporting that neither the incidence nor severity of AHSR were reduced by premedication).) Indeed, no anaphylaxis was seen during the Phase I trials conducted without premedication, as Defendants' clinical expert conceded. (Tr. 1035:13-18 (Calvert).) Steroid premedication is given (orally) with Taxotere not to prevent anaphylaxis (which rarely occurs), but rather to reduce the severity of mild hypersensitivity reactions like fluid retention (edema). (Tr. 1100:25-1101:23 (Childs).)[6] Because the incidence of anaphylaxis is the same with or without premedication, Dr. Williams' admission that Defendants' perfusions have a reasonable expectation of being administered without anaphylactic manifestations *with* premedication necessarily implies that those perfusions are equally capable of being administered *without* anaphylactic manifestations without premedication.[7]

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[6] The oral steroid premedication may thus be contrasted with the *intravenous* premedication with antihistamines and steroids given with the Taxol formulation. It is the latter, Taxol premedication regime and not the oral steroid regimen used with Taxotere, which is intended to reduce the incidence of anaphylaxis. (Tr. 1119:10-22, 1124:20-1125:3 (Childs).)

[7] Defendants' Dr. Calvert asserted that so long as *any* anaphylaxis occurs, there cannot be a reasonable expectation of avoiding anaphylaxis. (Tr. 990:5-14.) But this testimony simply reads the term "reasonable expectation" out of the claim construction, and ignores the teachings of the '561 patent specification, which describes anaphylaxis as having been "greatly reduced" by the claimed invention, not eliminated entirely. (JTX 3 at 2:28-30).

45. Defendants' clinical expert, Dr. Calvert, asserted that Defendants' perfusions do not have a reasonable expectation of being administered without anaphylactic manifestations because some hypersensitivity reactions still occur with Taxotere, and thus will occur with Defendants' perfusions. (Tr. 1021:24-1022:4.) However, in doing so, Dr. Calvert failed to distinguish between anaphylaxis and other different, and much less serious, hypersensitivity reactions.

46. At the time of the invention (July 1991), anaphylaxis was a distinct medical condition defined as a Grade 4 acute hypersensitivity reaction. (Tr. 117:22-118:3; 118:12-25 (Burris); 1393:3-9 (Handy).) In Dr. Calvert's words: "[a]naphylaxis is the most acute form of acute hypersensitivity reactions. Normally, it is graded as Grade 4, acute hypersensitivity reaction." (Tr. 976:11-13.) Although a patient experiencing anaphylaxis may exhibit a variety of symptoms, the cardinal sign of anaphylaxis is the rapid onset of vascular or circulatory collapse, which is what makes anaphylaxis a life-threatening emergency. (Tr. 112:20-113:13 (Burris); 1093:9-16 (Childs); 1389:25-1390:25, 1394:23-1395:5 (Handy).) Anaphylaxis itself is undeniably rare with Taxotere, as Dr. Calvert acknowledged. (Tr. 988:17-22.)

47. Dr. Calvert's application of "anaphylactic manifestations" to encompass hypersensitivity reactions *other than* anaphylaxis is incorrect. "Anaphylactic manifestations" are the symptoms manifested by a patient experiencing anaphylaxis. (Tr. 1090:25-1091:20 (Childs); 1393:10-22 (Handy).) That is, if a patient does not have anaphylaxis, he or she is not experiencing anaphylactic manifestations. (Tr. 1096:11-24 (Childs).) This is confirmed by the specification, which refers to avoidance of the "anaphylactic reactions" or "anaphylactic shock phenomena" seen with the prior art Cremophor-based formulations. (JTX 3 at 2:25-30, 48-51.)[8] The patent

[8] Defendants' expert, Dr. Myrdal, conceded that "anaphylactic reactions are reactions to a formulation that gives the patient anaphylaxis." (Tr. 956:5-7.)

never refers to hypersensitivity reactions generally and never indicates that the claimed invention is intended to avoid *all* hypersensitivity reactions. Thus, proper application of the claim term requires determination of whether there is a reasonable expectation of administering the perfusion without *anaphylactic* manifestations—the symptoms experienced by a patient suffering anaphylaxis.

REDACTED

C. Claim 5 Is Not Invalid

48. Defendants assert that Claim 5 is invalid under 35 U.S.C. §§ 102, 103, and 112. Claims are presumed valid. 35 U.S.C. § 282. Thus, invalidity must be shown by clear and convincing evidence. *TypeRight Keyboard Corp. v. Microsoft Corp.*, 374 F.3d 1151, 1157 (Fed. Cir. 2004).

49. The date of invention for both Patents-in-Suit is July 8, 1991, when the French application 91 08527 was filed. (JTX 12/12-T.) That application describes the invention and its properties, including the physical stability of the perfusion and the ability to use the formulation without anaphylactic or alcohol intoxication manifestations. Defendants do not appear to dispute the priority date. (Tr. 1171:8-9 (statement of James Hurst, counsel for Hospira) (referring to "the date we care about in this case, July 1991").) As evidenced by the file histories, the priority chain was unbroken from the French application to the applications that became the Patents-in-Suit. (JTX 2 at SA00012730 ('512 patent); JTX 4 at SA00012908 ('561 patent).)

50. It is undisputed that the date of application in the United States was July 3, 1992, the date of the twin PCT filings that led to each of the Patents-in-Suit.

51. A person of ordinary skill in the art with respect to the Patents-in-Suit holds a bachelor's of science degree with two to four years of experience in pharmaceutics and drug development, or a Ph.D. with commensurate experience to obtain the training and background necessary to understand the development of pharmaceutical formulations. (*See* Tr. 1437:10-15 (Park).)

1. Claim 5 Is Not Anticipated

52. Under 35 U.S.C. § 102, Defendants must show by clear and convincing evidence that a single prior art reference discloses all the elements of the invention, either expressly or inherently. *See, e.g., Schumer v. Lab. Computer Sys., Inc.*, 308 F.3d 1304, 1315 (Fed. Cir. 2002); *Forest Labs., Inc. v. Ivax Pharms., Inc.*, 438 F. Supp. 2d 479, 486 (D. Del. 2006).

53. Defendants cite to two categories of prior art in asserting anticipation of Claim 5: (1) Cremophor-based taxane formulations (the '470 patent and Rowinsky); and (2) failed efforts to develop a Cremophor-free taxane formulation (the Tarr article). These are taken up below.

a) The Cremophor-Based Prior Art ('470 Patent and Rowinsky)

54. U.S. Patent No. 4,814,470 (JTX 9) discloses docetaxel formulated in Emulphor—a different brand name for the same surfactant, Cremophor. (*See* Tr. 836:8-837:8 (Myrdal).) There is no mention of polysorbate anywhere in the '470 patent. (Tr. 1213:5-9 (Williams); 1487:4-6 (Park).) The Rowinsky article (JTX 15) similarly discloses paclitaxel formulated in Cremophor. Here too, there is no mention of polysorbate. (Tr. 1223:6-9 (Williams).) Both references were disclosed during prosecution, (JTX 3, cover page; *id.* at 1:40-2:36), and Defendants accordingly face a formidable burden in relying upon those references to invalidate Claim 5. *Impax Labs., Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366, 1378 (Fed. Cir. 2006).

55. This Cremophor-based prior art fails to anticipate for two separate reasons. *First*, polysorbate is essential to the operability of the invention because it is only the micelles formed by the polysorbate that allow for docetaxel to be carried through the bloodstream to the tumor. (Tr. 636:24-637:6 (Kaler).) The patent teaches the ratio of polysorbate to taxane necessary to achieve adequate physical stability. (JTX 3 at 2:37-45.) Thus, Claim 5 must "contain" some amount of polysorbate, just as the claim's plain text provides, with the amount of polysorbate necessary for any particular docetaxel concentration determined by routine stability testing, as

Dr. Myrdal acknowledged. (*See* Tr. 941:10-14.) The Cremophor-based prior art, which contains *zero* polysorbate, thus cannot anticipate Claim 5.

56. *Second*, Cremophor-based perfusions do not meet the claim limitation of having a reasonable expectation of being administered without causing anaphylactic manifestations. As Dr. Myrdal conceded, it is recognized in the technical literature that Cremophor-based formulations, but not polysorbate 80 ones, are associated with anaphylactic shock requiring pre-treatment with antihistamines. (Tr. 953:4-15.) And Dr. Williams, in testifying that the Cremophor-based formulations anticipated Claim 5, conceded that he was not considering the limitation that the perfusion be capable of administration without anaphylaxis. (Tr. 1254:14-25.) As noted above, Taxol—the commercially available Cremophor formulation—presented an unduly high incidence of anaphylaxis when administered without premedication, requiring the initial Phase I trials to be halted. (*See supra* ¶¶ 3-4.) Even with premedication specifically designed to prevent it, patients receiving Taxol are at significant risk of anaphylaxis, and special precautions still must be taken. (Tr. 138:1-21 (Burris); 1404:25-1405:7 (Handy).) In spite of these precautions, one medical safety watch group reported instances of anaphylaxis caused by Taxol, and suggested that these events are widely underreported. (Tr. 139:1-140:23 (Burris); PTX 444 at 133.)

57. As noted, the patent specifically describes the claimed invention as an improvement over the Cremophor prior art on the basis that the problems with anaphylaxis were avoided. (*See supra* ¶ 30.) "[I]t would be peculiar for the claims to cover prior art that suffers from precisely the same problems that the specification focuses on solving." *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1343-44 (Fed. Cir. 2005). Defendants cannot prove by clear and convincing evidence that the Cremophor-based formulations anticipate the limitation of avoiding

anaphylaxis. To the contrary, the trial record refutes any such assertion.

b) The Tarr Article

58. Defendants assert that the 1987 Tarr article (JTX 16) anticipates Claim 5. Tarr describes paclitaxel formulated in a "cosolvent system with 60% pluronic L64, 30% ethanol, and 10% polysorbate 80." (*Id.* at 31.) Here, too, Tarr was disclosed to the Examiner, presenting Defendants with a formidable challenge in seeking to invalidate the claim on this basis.

59. *First*, Tarr does not disclose a "perfusion." As noted above, the Examiner allowed Claim 5 over Tarr because, as Tarr itself reports, that paclitaxel formulation was not stable long enough to be used as a perfusion. (*See supra* ¶ 26.) Indeed, the Applicants submitted testing conducted on the Tarr formulation showing that it did not work. (*Id.*) Defendants have introduced no testing of their own and do not dispute the accuracy of Applicants' tests.

60. *Second*, Defendants provide no evidence that the Tarr formulation is capable of being injected without anaphylactic manifestations, or indeed is safe at all for intravenous use. Even today, pluronic L64—the primary surfactant used in Tarr—has never been approved for use in an intravenous infusion. (Tr. 1231:18-23 (Williams).) Dr. Williams conceded that testing would need to be performed before the toxicity of a pluronic L64-based taxane formulation could be ascertained. (Tr. 1233:11-14.) Defendants lack *any* evidence, let alone clear and convincing evidence, that the Tarr formulation would have a reasonable expectation of being administered without anaphylactic manifestations, or be tolerable in any sense.[9]

61. For the same reason, Defendants also lack evidence that the Tarr article is enabling. Dr.

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[9] Because Defendants objected to introduction of evidence concerning the toxicity of pluronic L64 as irrelevant (Tr. 1349:12-1350:9), they should be *precluded* from asserting that Tarr describes a *non-toxic* perfusion capable of being administered without anaphylactic manifestations.

Williams conceded that the "suitability of the Tarr formulation for infusion into patients is going to depend first and foremost upon the toxicity of pluronic L64" and that information about that toxicity was lacking. (Tr. 1233:11-14, 1235:17-1236:2.) The absence of evidence showing that the Tarr article discloses perfusions suitable for infusion into patients also defeats anticipation. *See Union Oil Co. of Cal. v. Atl. Richfield Co.*, 208 F.2d 989, 995-96 (Fed. Cir. 2000) (claims drawn to "gasoline suitable for combustion" in a certain type of engine not anticipated by prior art disclosing gasoline *not* suitable for combustion in that type of engine); *Rowe v. Dror*, 112 F.3d 473, 479-81 (Fed. Cir. 1997) (claims limited to "balloon *angioplasty* catheters" not anticipated by prior art reference not shown to be "suitable" for angioplasty procedures).

c) The G-V Reference

62. A 1991 publication in the *Journal of Medicinal Chemistry* ("G-V") reports *in vitro* tests evaluating the activity of various taxanes. (JTX 93.) The last sentence of the text states: "Moreover taxotere (13a) showed a better solubility in excipient system (polysorbate 80/ethanol, 1:1) than the two others [sic] most active compounds taxol (1) and *N*-debenzoyl-*N*-(*tert*-butoxycarbonyl)taxol (16a)." (*Id.* at 996.) To the extent Defendants intend to rely on this reference as anticipatory, any such argument should be rejected for the reasons set forth below.

63. *First*, G-V addresses only *in vitro* testing, as Dr. Myrdal agreed. (Tr. 957:4-11.) This is clear from the article: "The potential antimitotic activities of these new compounds have been investigated by using the *in vitro* tubulin assay. For some of the compounds, the *in vitro* cytotoxic properties were also determined." (JTX 93 at 993.) The docetaxel solution used for *in vitro* testing has nothing to do with clinical formulation development and a person of skill in the

art would not understand G-V to relate to a clinical formulation at all.[10] (Tr. 1462:17-1464:12 (Park).) G-V also never refers to or otherwise describes a perfusion, does not mention dilution in perfusion fluid, and does not indicate anything about the physical stability or other parameters of a perfusion. (Tr. 959:4-18 (Myrdal).) Nor does G-V disclose concentrations of either polysorbate 80 or ethanol within the limits of Claim 5, and the concentration of docetaxel disclosed is 1,000 times too small to be suitable for use in a perfusion. (Tr. 1460:11-1462:4 (Park); *see also* Tr. 957:4-20 (Myrdal).) In short, G-V does not disclose a perfusion at all, let alone describe one in clear and convincing fashion.

64. Defendants suggested that a person of ordinary skill in the art would infer that G-V was describing a perfusion because polysorbate and ethanol are not suitable for *in vitro* testing. Defendants err as a matter of fact: both polysorbate and ethanol are routinely used for *in vitro* work. (Tr. 1458:24-1459:5 (Park).) Defendants also err as a matter of law: anticipation requires the claim to be disclosed in the anticipating reference itself; gaps in the disclosure cannot be made up through such extrinsic evidence. *See Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1473 (Fed. Cir. 1997) ("An expert's conclusory testimony, unsupported by the documentary evidence, cannot supplant the requirement of anticipatory disclosure in the prior art reference itself."); *see also Finnigan Corp. v. ITC*, 180 F.3d 1354, 1365-66 (Fed. Cir. 1999) (expert testimony that one skilled in the art may see missing element as present held insufficient). Defendants' reliance on such extrinsic testimony here simply emphasizes what is,

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[10] G-V contains one reference to animal testing in "grafted murine tumors," immediately above the sentence mentioning polysorbate 80, (JTX 93 at 996), which Defendants tellingly ignore. (Tr. 1278:13-24 (Williams).) The animal testing cited in G-V was work done by M. Lavelle. (JTX 93 at 995 n.25.) As M. Lavelle reported in the file history of the '470 patent, which was available to a person of ordinary skill in the art before 1991, the animal testing reported in G-V was done with an Emulphor-based formulation. (JTX 10 at SA01005349.) This would further confirm that the *in vitro* testing reported in G-V had nothing to do with actual formulation work.

in truth, entirely absent from G-V: namely, any description of a perfusion.

65. *Second*, the subject matter of the sentence upon which Defendants rely is not related to formulation of a perfusion, which instead depends upon issues of physical *stability*, not *solubility*. (Tr. 959:4-13 (Myrdal).) Indeed, the perfusions at issue in this case are supersaturated: that is, the taxanes are not entirely soluble in the perfusion fluid. Instead, the claimed perfusions depend upon their minimum physical stability, the length of time before the taxane precipitates. Comparative solubility does not relate to this issue, as Dr. Williams conceded. (Tr. 1245:11-23; *see also* JTX 16 at 31 ("Even if a compound has adequate solubility in a nontoxic cosolvent system, it does not necessarily mean the formulation is acceptable. The major problem encountered in cosolvent systems is that the drug may immediately precipitate upon admixture with water, saline or blood.").) Thus, a person of ordinary skill would not read the article's reference to solubility as having any applicability to the formulation of a perfusion, let alone actually disclosing such a perfusion. (Tr. 1463:19-1464:3 (Park).)

2. Claim 5 Is Nonobvious

66. To render Claim 5 obvious pursuant to 35 U.S.C. § 103(a), Defendants must prove two separate propositions by clear and convincing evidence (*see supra* ¶ 48). *First*, Defendants must prove that it would have been obvious to formulate taxanes using polysorbate 80 for intravenous administration despite the established use of Cremophor at the time for formulating taxanes specifically and for intravenous formulations generally. (*See* supra ¶ 8.) It is not enough for Defendants to assert that polysorbate *itself* was a prior art surfactant. "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex*, 550 U.S. 398, 418 (2007). Defendants must instead show clearly and convincingly "an apparent reason to combine the known elements in the fashion claimed by the patent at issue", in light of the prior art as a whole,

the effects of demands known to the relevant community or present in the marketplace, and the background knowledge possessed by a person of ordinary skill in the art. *Id.*[11]

67. *Second*, Defendants must separately prove that, if a person of ordinary skill undertook to make this combination, he would have done so with a reasonable expectation of success. *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1363 (Fed. Cir. 2009) (claim was nonobvious when one would have expectation of success only in hindsight).

68. With respect to the doctrine of "obvious to try", if there is no proof that there were (in the words of *KSR*, 550 U.S. at 420) a "number of identified, predictable solutions" in the prior art to the identified problem, that weighs against a finding of obviousness. *See, e.g., In re Omeprazole Patent Litig.*, 536 F.3d 1361, 1380 (Fed. Cir. 2008) (affirming finding of nonobviousness when district court "gave lengthy consideration to the multiple paths that would have faced a person of ordinary skill in the art who recognized" the problem to be solved). In an unpredictable art, such as the chemical arts, results are more likely to be unexpected and therefore nonobvious. *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008). In addition, "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *KSR*, 550 U.S. at 416.

a) The Prior Art Did Not Teach Formulation of Taxanes With Polysorbate

69. Defendants face a formidable hurdle in that formulation work in general, and formulation of poorly water soluble compounds in particular, is an unpredictable enterprise. Defendants'

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[11] "The *KSR* Court acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination. . . . As long as the test is not applied as a 'rigid and mandatory' formula, that test can provide 'helpful insight' to an obviousness inquiry.'" *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (*quoting KSR*, 550 U.S. at 419).

expert, Dr. Williams acknowledged that "drug formulation is an important and highly empiric endeavor to prepare pharmaceutic agents in a form that are stable and can be administered and tolerated by patients", and that "trial and error, especially during the multiple stages of Phase I, II and III clinical trials development, are the norm in hydrophobic drug formulation challenge." (Tr. 1251:6-1252:7.) As Dr. Park explained, "[o]ne of the characteristics of a poorly [water] soluble drug is you just cannot predict" beforehand whether a formulation would work. "[T]here is no theory telling you this particular drug, you have to use this formulation . . . . In the absence of a theory, we don't know what to expect". (Tr. 1440:25-1441:14.)

70. Adding to the unpredictability of formulating taxanes is the fact that there are many different formulation approaches that can be explored. (*See supra* ¶ 68.) For example, although the '470 patent only enables use of an Emulphor-ethanol formulation with docetaxel, (Tr. 1213:5-14 (Williams)),[12] that patent also suggests that a formulator seeking an alternative would be faced, *ex ante*, with innumerable options to try. (JTX 9 at 9:27-41.) Defendants have even acknowledged that formulating taxanes is particularly challenging. (Tr. 807:1-5, 811:8-21 (Liu); *see also infra* ¶ 82.) And, the inventors explored several different pathways (microemulsions, cosolvent systems, intralipid systems, and mixed micelles) before settling upon the polysorbate-based formulation. (*See supra* ¶¶ 6, 12.) Many of these different approaches failed before the inventors succeeded with polysorbate. (Tr. 935:7-938:24 (Myrdal); PTX 413 at 170.)

71. Defendants' principal contention is that the prior art taught a "surfactant swap"—that is, taught a skilled artisan to substitute polysorbate for Cremophor in formulating taxanes.

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[12] *Cf. Pharm. Res., Inc. v. Roxane Labs., Inc.*, 253 Fed. App'x 26, 29-31 (Fed. Cir. 2007) (unpublished) (claim with "extraordinary broad scope" such as would cover "hundreds of possible surfactants" was not enabled, when specification disclosed "only three working examples, utilizing only one new surfactant").

Defendants rely on certain prior art disclosing the "etoposide" formulation for this contention. However, neither the etoposide prior art nor any other cited art teaches such a "surfactant swap" or otherwise renders obvious the use of polysorbate in formulating a taxane perfusion.

72. For several reasons, the etoposide prior art did not teach a "surfactant swap." To the contrary, as Defendants' Dr. Myrdal conceded, what the etoposide prior art disclosed was a specific formulation used for formulating etoposide—the "VP-16" formulation—that included a variety of excipients, including a small amount of polysorbate 80 along with benzyl alcohol and other solvents. (Tr. 921:17-922:20 (Myrdal).) Thus, rather than describing a general approach of substituting polysorbate for Cremophor in any formulation, the art instead simply describes a particular formulation that worked for etoposide (which is not a taxane). In Dr. Myrdal's own words, the prior art describes "using the etoposide formulation instead of the Cremophor-based formulation." (Tr. 921:24-25; *see also* Tr. 1503:22-1505:7 (Park).)

73. This distinction is important because the record demonstrates that VP-16, the etoposide formulation, would *not* work for taxanes. The inventors tried the etoposide formulation for docetaxel, but it failed because the docetaxel precipitated too quickly (that is, the perfusion did not have sufficient physical stability). (*See supra* ¶ 12.) In addition, the etoposide formulation includes benzyl alcohol, which is incompatible with taxanes. (Tr. 794:9-795:1 (Liu).) The fact that the etoposide formulation—the only intravenous formulation cited by Defendants in actual clinical use that included any polysorbate—does not work for taxanes would teach away from using polysorbate in formulating taxanes; it assuredly does not render the claims obvious. *See Medinol Ltd. v. Guidant Corp.*, 412 F. Supp. 2d 301, 324-25 (S.D.N.Y. 2005) (denying summary judgment of obviousness because, *inter alia*, prototype embodying defendant's prior art combination had been tried and failed).

74. Defendants attempt to compensate for the failure of etoposide by arguing that it would be obvious to change the etoposide formulation to increase the polysorbate *by at least a factor of five* and delete the benzyl alcohol—modifications Defendants describe as mere "optimization." Strikingly absent from the record is any prior art teaching such "optimization." To the contrary, the cited art uses the etoposide formulation without change, even when applying that formulation to a new drug, such as acronycine. In fact, such dramatic modifications to the etoposide formulation would not be attempted by a person of ordinary skill, among other reasons because a five-fold change in polysorbate concentrations would raise substantial toxicity and tolerability concerns. (Tr. 1332:5-1333:24 (Rodricks) (such a change would not be "optimization" but could "raise new issues that were not seen with the earlier lower dose" requiring testing); 1469:5-1470:6 (Park) (rather than "optimization", change would constitute "entirely different formulation").) In fact, as Hospira's formulator confirmed, a skilled artisan would know that changing the amount of polysorbate from a prior formulation could also result in a change in the safety and effectiveness profile in the new formulation. (Tr. 793:9-794:8 (Liu).)[13]

75. Indeed, the fact that a "surfactant swap" of polysorbate for Cremophor was *not* obvious is demonstrated by the standard reference cited by Defendants—the Handbook of Injectable Drugs. As that reference makes clear, the standard surfactant for use in intravenous formulations was Cremophor, and even when a drug as formulated in polysorbate for other uses (such as intramuscular injection), Cremophor would be used for intravenous infusions. (*See supra* ¶ 8.)

76. That the use of polysorbate to formulate taxanes was not obvious is confirmed by the

[13] Defendants are also factually incorrect when they assert that the only difference between etoposide and teniposide is the "surfactant swap." There were several changes in excipients between the two formulations, (Tr. 1467:4-1469:8 (Park)), and Defendants' experts never even addressed whether a skilled artisan would have considered those other changes to be the reason why etoposide had a better side-effect profile than teniposide.

Tarr article (JTX 16), upon which Defendants erroneously rely. In addition to the differences identified above, (*see supra* ¶ 58-61), Tarr does not render Claim 5 obvious because it was a failure, as the article states and as Dr. Myrdal conceded. (Tr. 950:7-951:8; *see also supra* ¶ 59, 67.)[14] As a failed taxane formulation, it would teach away from the claimed invention.

77. Defendants attempt to diminish the consequence of Tarr by arguing that it was simply an "academic" exercise. This is incorrect. The work reported in Tarr came at a time when paclitaxel was in short supply and a Cremophor-free formulation urgently needed. Accordingly, paclitaxel would not have been used for mere academic exercises. (Tr. 1240:7-16 (Williams); 1452:25-1453:18 (Park).) In any event, the teachings of Tarr—including its express conclusion that the disclosed formulation was unsuitable for taxanes—are unambiguous. Especially given his prominence in the field, (Tr. 1239:16-19 (Williams); 1448:24-1449:3 (Park)),[15] Dr. Yalkowsky's failed use of a double-surfactant system (pluronic L64 and polysorbate), would have been understood by a skilled artisan to indicate that a simpler, single surfactant system (such as polysorbate alone) *would not have worked.* (Tr. 1455:1-1456:2; 1457:5-14 (Park).)

78. Defendants' obviousness contention boils down to the inherently implausible position that Dr. Yalkowsky tried and failed a combination of pluronic L64 and polysorbate 80 when it was obvious (according to Defendants) to use polysorbate 80 alone. Dr. Yalkowsky's failure even to mention the possibility of successfully formulating taxanes in polysorbate 80 alone refutes any argument that such a formulation was obvious; his failed attempts to formulate

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[14] Dr. Williams erroneously disregarded any requirement that the formulation disclosed in Tarr be suitable for intravenous use, either with regard to physical stability or toxicity, despite the Examiner's allowance of the claims over Tarr. (Tr. 1236:13-1237:23; 12:41:9-13; *but see supra* ¶¶ 25-32; *see also supra* ¶ 59-61.)

[15] As Dr. Myrdal testified, if Dr. Yalkowsky wrote something, it was believed. (Tr. 946:6-8.)

taxanes without Cremophor negate any reasonable expectation of success. *Boehringer Ingleheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003) ("there can be little better evidence negating an expectation of success than actual reports of failure.")

79. The deficiencies in Defendants' obviousness challenge are not remedied by the G-V reference. As discussed above, (*see supra* ¶ 62), that reference does not discuss perfusions at all, let alone suggest that polysorbate could be used to formulate taxanes for intravenous use. The sole issue discussed in the single sentence in G-V relied upon by Defendants, solubility, is simply unrelated to formulation of perfusions, (*see supra* ¶ 65), and the sort of concentrations described in G-V have no relevance to formulation work (Tr. 958:8-959:18 (Myrdal).) G-V thus provides neither a reason for making an intravenous taxane formulation with polysorbate nor a reasonable expectation of success in doing so. It provides no support (let alone clear and convincing support) for Defendants' obviousness challenge.

b) Defendants Failed To Prove Reasonable Expectation of Success

80. To show a reasonable expectation of success in using polysorbate with a taxane, Defendants must also overcome the clinical record of polysorbate as of 1991, which was unfavorable. As noted above, the literature raised concerns about the toxicity of polysorbate in a perfusion, both generally and particularly in comparison to Cremophor, and even when used in much lower concentrations than would be required with a taxane. (*See supra* ¶ 7.) In addition to the "E-Ferol" disaster noted above, (*see supra* ¶ 8; Tr. 1330:18-1332:4 (Rodricks)), there was also the "amiodarone" formulation, where it was thought that its relatively small amounts of polysorbate adversely affected the blood pressure of patients taking the drug. (Tr. 1325:25-1328:10 (Rodricks); PTX 356).) A separate prior art study suggested that polysorbate 80, when administered intravenously (as opposed to orally) depressed the blood pressure of, and caused histamine release in, dogs. (Tr. 1328:11-1330:17 (Rodricks); PTX 366).)

81. Polysorbate was not a common surfactant for intravenous formulations at the time of the invention, as the parties' witnesses all agreed. (*See supra* ¶ 8.) As Dr. Myrdal indicated, Cremophor was the surfactant of choice. (Tr. 917:10-17; *see also* 1473:7-23, 1486:10-20 (Park).) Nothing in the prior art provided a reasonable expectation of success in using polysorbate to formulate taxanes, either with regard to achieving the necessary physical stability or with regard to the safety and effectiveness of the formulation. To the contrary, the prior art showed failures in formulating taxanes with regard to all of these factors—a clear negation of any reasonable expectation of success. *Boehringer Ingleheim*, 320 F.3d at 1354.

82. The nonobviousness of Claim 5 (and the other asserted claims) is further shown by the testimony and representations made by Hospira in connection with its own formulation. Ms. Liu, Hospira's formulator, testified that formulating docetaxel was difficult, including the challenge presented by the compound's near insolubility in water. (Tr. 807:1-5, 812:3-17; *see also* 1442:5-19 (Park).) So difficult is formulating docetaxel that Hospira has filed a patent application on its own formulation, with a priority date 14 years *after* the Patents-in-Suit. (PTX 19.) In seeking a patent, Hospira described to the Patent Office the difficulties in formulating docetaxel, including the difficulties that the inventors encountered in developing the formulation patented in the '561 and '512 patents:"[d]ue to the fact that docetaxel is practically insoluble in water, there have been numerous attempts to develop appropriate injectable formulations. This difficulty in formulating docetaxel is one of the reasons for the delay between its discovery and its first approval for use in 1996". (*Id.* at SA01000756.) These representations made by Hospira to the PTO directly negate its obviousness challenge here, and make plain that developing a Cremophor-free formulation of docetaxel in 1991, as sanofi-aventis did, was not obvious. Surely, if the minor changes made to Taxotere by Hospira are patentable as of 2005, then the

fundamental innovation made by the inventors, to formulate taxanes as a perfusion without using Cremophor fourteen years earlier, is indisputably nonobvious.

c) Objective Indicia of Nonobviousness Support the Validity of Claim 5

83. Objective indicia of nonobviousness "may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538-39 (Fed. Cir. 1983) (citation omitted).

(1) Long-Felt Need/Failure of Others

84. If the claimed invention solves a long-felt need, that suggests nonobviousness. *See, e.g.*, *Alza Corp. v. Andrx Pharms., LLC*, 607 F. Supp. 2d 614, 648 (D. Del. 2009). Similarly, failure by others of skill in the art who attempted to fill that long-felt need also suggests nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

85. Here, in light of the fatal results of the 1984 Phase I trials of paclitaxel, there was an urgent need for a Cremophor-free taxane formulation. (Tr. 125:17-128:15 (Burris); PTX 553 at 607.)[16] Efforts to find such a formulation were reviewed by Dr. Yalkowsky, who observed that "[f]or the past eight years, a number of investigators have attempted to develop more pharmaceutically acceptable formulations for this compound that eliminate Cremophor and do not precipitate upon dilution". (PTX 413 at 170; *see also* Tr. 933:7-951:23 (Myrdal).) The work reviewed by Dr. Yalkowsky began in the mid-1980s—shortly after the problems with

[16] The failures with paclitaxel are particularly relevant here because, as Dr. Myrdal acknowledged, a person of ordinary skill would look to the paclitaxel work as guidance for what would work for docetaxel as well. (*See* Tr. 930:25-931:18.)

anaphylaxis were discovered with the Cremophor-based Taxol formulation—and continued into the 1990s. (Tr. 935:7-938:24 (Myrdal); 1452:5-1453:12 (Park); *see also* Tr. 123:3-124:1 (Burris).) All of these attempts failed, producing compositions that were insufficiently stable, too toxic, or both. None succeeded until the named inventors here, who filed for their patent in July 1991. This half-decade of failures prior to the inventors' success is compelling evidence that what the inventors achieved was not obvious.

(2) The Prior Art Taught Away from Using Polysorbate

86. "[T]eaching away," is one of the objective indicia of nonobviousness. *Telcordia Techs., Inc. v. Cisco Sys., Inc.*, 592 F. Supp. 2d 727, 742 (D. Del. 2009) (Sleet, J.). The teaching away here is express. In 1990, following the efforts reviewed above to find a Cremophor-free taxane formulation, the leading researchers in the field wrote that "there is no suitable substitute for Cremophor EL in taxol formulation." (JTX 145 at 1267; *see also* Tr. 246:14-247:25 (Burris).) This conclusion expressly teaches away from using polysorbate as a substitute for Cremophor; indeed, it expressly negates the notion that a "surfactant swap" was obvious.

87. In addition to the express teaching away in the Weiss article, the prior art further taught away from formulating taxanes in polysorbate by indicating that polysorbate would not work for taxanes. This is the clear inference, as discussed above, from Tarr, which reported failure for a system with pluronic L64, ethanol, and polysorbate 80. That polysorbate 80 would fail was also taught by published literature concerning activity testing on taxanes. As early as 1981, the literature (specifically the Miller '221 patent, JTX 135) showed that the activity of paclitaxel was

significantly decreased when it was injected with polysorbate 80 rather than Cremophor.[17] (Tr. 1520:15-1523:7 (Park).)

88. Defendants' expert, Dr. Williams, conceded that "a person of ordinary skill in the art would try to avoid . . . an excipient [that] is believed to interfere with the activity of the drug substance". (Tr. 1271:21-1272:12.) Yet the prior art goes beyond that, showing not merely that polysorbate 80 substantially reduced the activity of taxanes compared to Cremophor, it actually reduced Taxol activity to the level of the drug cephalomannine, which was reported in the prior art to have no useful antitumor activity at all. (Tr. 1484:15-1485:17 (Park); PTX 719 at 390.)[18]

89. The belief that polysorbate would not work for taxanes was bolstered by evidence suggesting that Cremophor played a role in taxane activity—namely by reversing "multi-drug resistance," the tendency of tumor cells to build resistance to many different drugs as their exposure to those drugs accumulates. Taxanes are particularly susceptible to being pumped out of tumor cells by a transport protein called P-glycoprotein, a phenomena known as the P_gP efflux pump. (Tr. 1471:7-1473:6 (Park).) The prior art attributed Cremophor with the ability to inhibit the P_gP efflux pump, reversing the tumor cells' resistance to chemotherapies using taxanes and increasing their effectiveness, (*e.g.* PTX 419; PTX 420), suggesting that Cremophor was necessary for taxane formulation and teaching away from the use of polysorbate.

90. The fact that the prior art taught away from using polysorbate is confirmed by a 2001 review article by van Zuylen and others, (PTX 209), which observed that "in early studies conducted by the National Cancer Institute, paclitaxel was not effective in several tumor models

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[17] *Compare* JTX 135 at col. 7, tbl. V (reporting antitumor activity against P388 tumor of taxol in polysorbate at 152%) *with* PTX 334 at SA01000933, tbl. 19 (reporting antitumor activity against P388 tumor of taxol in Cremophor at 190%).)

[18] In PTX 719, cephalomannine is described by its alternative name "Taxol B."

when given intravenously as a solution in polyethyleneglycol 400 or 10 to 15% Tween 80-ethanol, *suggesting that the CrEL-based [i.e., Cremophor-based] vehicle is essential for in vivo antitumor activity.*" (PTX 209 at 135 (emphasis added).)

91. Defendants suggested at trial that the van Zuylen article was simply wrong, based on its citation to a 1992 Rose article, (JTX 94), which purportedly shows that polysorbate does work for taxanes. But it is Defendants who have misread the references. For demonstrating that polysorbate does work, the Rose article cites the inventors' own work, the "Bissery" article, which reported on activity testing with the Taxotere formulation in September 1991, after the priority date of the patents in suit. (JTX 94 at 311, *citing* JTX 138; *see also* Tr. 1517:5-17 (Park).) In other words, Rose could say in 1992 that polysorbate worked with a taxane *only because the inventors proved, for the first time, that it worked.* By contrast, (and as van Zuylen correctly notes), before the inventors' discovery, the published work showed that polysorbate did *not* work (such as reported in Miller discussed above). In any event, it is van Zuylen, and not Defendants' litigation-motivated testimony, that correctly reports how the prior art was actually understood by those in the art—namely, that polysorbate would not work.

92. Indeed, Defendants have no logical explanation for why NCI and Bristol Myers did not either use polysorbate in the first place, or make the supposedly obvious "surfactant swap" to polysorbate after a patient died from Cremophor, (*see supra* ¶¶ 4-5.) The reason is clear: NCI and Bristol Myers thought polysorbate would not work (as did Dr. Yalkowsky, who instead unsuccessfully tried the combination of pluronic L64 with polysorbate). (Tr. 1518:14-1519:11 (Park).) Accordingly, real-world events confirm the truth of what was stated expressly in the 1990 Weiss article: that until the invention in 1991, those in the field believed that polysorbate would not work for taxanes. This too confirms the non-obviousness of the asserted claims.

(3) Unexpected Benefits

93. A finding that a patented invention demonstrates superior and unexpected benefits suggests non-obviousness. *Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1349 (Fed. Cir. 2004).[19] The unexpected benefits of the claimed invention are substantiated in the technical literature published since the development of Taxotere.

94. Since the development of Taxotere, it has been discovered that unlike Cremophor, polysorbate 80 is rapidly metabolized and hence removed from the patients' blood stream, reducing the likelihood of side-effects and drug-drug interactions. In the words of leading researchers in the field, "this much more rapid breakdown of PS-80 makes this compound a much more favorable component for the formulation/solubilization of poorly water-soluble agents than Cremophor EL." (PTX 208 at 301.)

95. The unexpected advantage of polysorbate 80 in metabolic breakdown has shown therapeutic advantages in the clinic, including reductions in "drug interactions and excipient-related toxic side effects." (PTX 214 at 509; Tr. 154:22-156:1 (Burris).). The unexpected linear pharmacokinetics of polysorbate 80 facilitates the administration of Taxotere in combination with other drugs by avoiding drug-to-drug interactions. (Tr. 159:8-160:9 (Burris).) Taxotere also exhibits less neuropathy than Taxol. (Tr. 149:20-150:23 (Burris); 1407:9-17 (Handy).)

(4) Commercial Success

96. An invention's commercial success is strong evidence of non-obviousness. *Glaxo Group Ltd.*, 376 F.3d at 1349. "When a patentee can demonstrate commercial success, usually shown

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[19] Defendants are incorrect to assert that the law requires unexpected results to be the *polar opposite* of conventional wisdom. Rather, the only requirement is that "the claimed invention exhibits some superior property or advantage that a person in the relevant art would have found surprising or unexpected." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995).

by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due" to the invention. *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997).

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98. Plaintiffs have shown that Taxotere practices all five of the asserted claims. (Tr. 541:17-542:5 (Kaler, '561 patent); Tr. 655:19-24, 674:21-675:17, 677:1-6 (Myerson, '512 patent).). Moreover, Defendants' expert Dr. Williams has conceded that Taxotere practices Claim 5. (Tr. 1258:10-18.) In any event, Defendants have barely attempted to rebut the resulting presumption that the commercial success is due to patented features. *See, e.g., Ecolochem Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1377 (Fed. Cir. 2000). In fact, it is undisputed that the lack of Cremophor in Taxotere is a major selling point. (Tr. 1076:14-22, 1080:22-1081:9 (Verini).)

99. There is no basis for saying that people use Taxotere solely because of the active ingredient as opposed to the formulation: "normally in a clinical setting when you're talking about patients, they speak about the drug. And in my mind the drug is all-inclusive of all those components" (the formulation and the active ingredient). (Tr. 1083:23-1084:6 (Verini).) Another reason people use Taxotere is linear pharmacokinetics, which as reviewed above, (*see supra* ¶ 95), is an unexpected benefit of the invention attributed to the presence of polysorbate 80 instead of Cremophor. (Tr. 1076:14-1077:2 (Verini).)

100. In light of the above, Plaintiffs have met their burden to show nexus, as it is not the Plaintiffs' burden to show that the product is successful *solely* because of the patented feature. *See, e.g., Rambus Inc. v. Hynix Semiconductor Inc.*, 254 F.R.D. 597, 602 (N.D. Cal. 2008).

(5) Copying

101. Copying of the claimed invention indicates nonobviousness. *See, e.g., Syngenta Seeds, Inc. v. Monsanto Co.*, 404 F. Supp. 2d 594, 601 (D. Del. 2005). Here, both Defendants simply took the formulation according to the Patents-in-Suit and then added PEG 300 and (in Hospira's case) citric acid as fillers. In fact, the "workhorse" of the perfusion, the polysorbate 80, (Tr. 542:6-543:14 (Kaler)), is present in *exactly* the same amounts and ratio as in Taxotere. (*See* JTX 313 at Hospira0049282; PTX 116 at API-DOC-0000339.)

3. Claim 5 Is Not Indefinite

102. A patent claim satisfies the definiteness requirement of 35 U.S.C. § 112 if a person of ordinary skill in the art would understand the bounds of the claim when read in light of the specification. In particular, a claim is definite if its scope can be measured through review of the specification combined with routine testing. *See, e.g., Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1378-80 (Fed. Cir. 2001); *In re Halleck*, 422 F.2d 911, 914 (C.C.P.A. 1970) (term "an effective amount" not indefinite: "[g]ranted that the proportions may vary for a specific agent and specific animal at a particular stage of growth, it does not appear from the facts of record that determination of such amounts would be beyond the skill of the art nor that it would involve undue experimentation to ascertain them").

a) Claim 5 Is Not Indefinite for Failing To Provide Explicit Lower Polysorbate and Ethanol Limits

103. With respect to polysorbate, the '561 patent discloses the proper ratio of docetaxel to polysorbate to achieve adequate stability. (*See* JTX 3 at 2:37-45.) Accordingly, whether a

particular ratio will fall within the scope of Claim 5 can be determined through routine stability testing to determine if the eight-hour minimum time for physical stability is achieved, as noted by Dr. Myrdal. (*See* Tr. 941:10-14; *see also Exxon*, 265 F.3d at 1378-1380 (term "for a period sufficient" not indefinite despite lack of explicit upper or lower boundary for the "period sufficient", when boundaries could be derived from the specification and routine testing).) This is confirmed by the fact that each Defendant was able to establish through routine testing, as demonstrated by their respective proposed labels, that their perfusions are physically stable for an equivalent of eight hours. (*See supra* ¶ 37.)

104. The absence of a explicit lower limit for ethanol does not render Claim 5 indefinite. The '561 specification itself discloses that the ethanol content according to the invention can be significantly reduced from the prior art. (JTX 3 at 2:37-42.) Moreover, U.S. Patent No. 5,403,858, (JTX 7), cited during prosecution of the '561 patent, makes express that it is unnecessary to use any ethanol to solubilize docetaxel. Thus, a skilled artisan would understand that, for Claim 5, the lower ethanol limit is zero, and (as with polysorbate) whether any particular perfusion infringes Claim 5 can easily be ascertained.

b) The Limitation "Without Anaphylactic . . . Manifestations Being Associated Therewith" Is Definite

105. "Anaphylactic manifestations" is readily understood to refer to "anaphylaxis" by any medical professional, (Tr. 1389:20-1390:25 (Handy)), and as noted above, this definition is fully supported by the language in the '561 patent. (*See supra* ¶¶ 41-47.) Dr. Calvert's assertion that the medical condition "anaphylaxis" cannot be understood by medical professionals flies in the face of reality. Medical professionals know how to accurately diagnose and treat anaphylaxis because if they do not, their patients will die. (Tr. 113:23-25 (Burris); 1394:24-1395:5 (Handy).)

106. Defendants suggest that Taxol and Taxotere are indistinguishable as to the incidence of

anaphylaxis. This is wrong. Oncology nurses, who administer these drugs to patients and are responsible for monitoring them for side effects, are trained in the differences between the drugs. While the literature instructs an oncology nurse to prepare for anaphylaxis in both Taxotere and Taxol administration as a precaution, it is a "defining characteristic" *only for Taxol.* (PTX 394 at 140, 257; PRX 902 at 53-54.) It is commonly understood in the oncology nursing community that anaphylaxis is only *expected* with the administration of Taxol, even with antihistamine and corticosteroid premedication. (Tr. 1401:25-1404:20 (Handy).) Moreover, as Dr. Childs testified, there have been less than ten occurrences of anaphylaxis out of over 300,000 patients receiving Taxotere. (*See supra* ¶ 43.) In contrast, anaphylaxis, including fatal anaphylaxis, remains a problem with Taxol, despite the fact that Taxol patients (unlike Taxotere patients) are premedicated with intravenous antihistamines specifically designed to reduce the incidence of anaphylaxis. (*See supra* ¶ 56.) Even Dr. Calvert admitted that, without premedication, there is a significant difference in the occurrence of anaphylaxis caused by Taxol and Taxotere, an indisputable point given the dramatic difference in outcome of the initial Phase I trials of the two. (Tr. 1035:13-1037:12; *supra* ¶ 44.)

c) The Limitation "Without . . . Alcohol Intoxication Manifestations Being Associated Therewith" Is Definite

107. All parties' experts acknowledged that a benchmark exists at which clinicians can recognize the blood alcohol content at which alcohol intoxication manifestations can occur. For example, Plaintiffs' expert Dr. Burris explained that the threshold for when a physician would have a "reasonable expectation" that alcohol intoxication manifestations would not occur from administration can be expressed in terms of a standard serving of alcohol to a person. (Tr. 180:6-25.) Dr. Williams expressed the "benchmark" that could be used in terms of blood alcohol content, specifically, 0.04 grams of alcohol per 100 milliliters of blood. (Tr. 1261:4-21.)

108. Defendants are also wrong to contend that there is no difference between Taxol and Taxotere regarding the incidence of alcohol intoxication manifestations caused by each drug. When administered in one hour in full dose, it was known in the oncology community that alcohol intoxication manifestations would result, and that this side effect was "one of the barriers to the development of Taxol." (*See* Tr. 1123:2-8 (Childs); *see also* PTX 467 at 499 ("[I]n patients receiving an equivalent dose of paclitaxel given as a 1 [hour] infusion, the plasma alcohol levels would likely be high enough for significant pharmacological effects to occur.").) The risk of alcohol intoxication manifestations therefore prevents Taxol from being administered at full dose over one hour. In contrast, there is no evidence that Taxotere causes alcohol intoxication manifestations, (Tr. 1122:13-1123:1 (Childs); *see also supra* ¶ 40), and it is therefore routinely administered as a one-hour full dose infusion.

4. Claim 5 Is Enabled

109. 35 U.S.C. § 112 provides that the specification must "enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use" the claimed invention. To be enabled, a patent must disclose enough information that a skilled artisan would be able to practice the invention without undue experimentation. *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991). The time frame for measuring enablement is as of the date of the United States filing (here, July 1992). *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1566 (Fed. Cir. 1991).

110. The definition of "anaphylactic manifestations" was set forth above. (*See supra* ¶¶ 46-47.) The '561 patent allows a person of ordinary skill to make and use perfusions avoiding these manifestations without antihistamine premedication, the medication recognized as essential to preventing anaphylaxis. Taxotere, which practices the asserted claims (as Defendants' expert Dr. Williams admitted, *see supra* ¶ 98), avoids these manifestations based on hundreds of thousands of data points (*see supra* ¶ 43).

111. For the reasons stated above, Defendants' experts ignore the '561 patent itself and the Court's claim construction when they maintain that in order for the patent to be enabled, Taxotere must *completely* avoid causing anaphylaxis. (*See supra* ¶¶ 41-47.) As of the date of U.S. filing, a person of ordinary skill in the art would readily understand that, as a result of clinical evaluation, the use of polysorbate in the claimed formulation "greatly reduced" the incidence of anaphylactic manifestations, just as the '561 patent states. (JTX 3 at 2:25-30.) Literature available before the U.S. filing date (July 3, 1992), as well as articles published shortly thereafter, confirmed that the invention could be made and used. (*See* PTX 506 at 453 ("[N]o immediate or early hypersensitivity reactions have been observed [with the administration of Taxotere]."); PTX 325 ("Taxotere is clearly an active new anticancer agent with manageable toxicities"); *see also* PTX 459 at 1040 (summarizing Phase I trial results and observing that "[u]nlike Taxol, Taxotere did not induce significant acute hypersensitivity reactions").)

III. CLAIMS 2 AND 10 OF THE '561 PATENT ARE INFRINGED AND NOT INVALID

A. Both Defendants Infringe Claims 2 and 10

112. Claims 2 and 10 of the '561 patent have four elements that differ only slightly as to element 3 (as noted in brackets below): (1) A composition; (2) consisting essentially of docetaxel dissolved in a mixture of ethanol and polysorbate; (3) is used to form [claims 2 and 10] or forms [claim 10] an injectable solution which contains up to 1 mg/ml of docetaxel; (4) capable of being injected without causing anaphylactic or alcohol intoxication manifestations. (JTX 3, cl. 2, 10; *see also* Tr. 521:7-523:2 (Kaler).)

113. Elements one and three are undisputed. Hospira's NDA product is a stock solution (a "concentrated solution" and a type of "composition").

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114.

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115. Both Defendants' perfusions can be administered with a reasonable expectation of avoiding anaphylactic and alcohol intoxication manifestations. (*See supra* ¶¶ 39-47.)

116. The final limitation of Claims 2 and 10 is "consisting essentially of." The Court has construed this term to mean "composed of the listed ingredients, and may include other ingredients that do not affect the basic and novel properties of the invention." (D.I. 347 at 2-3).

REDACTED

117. The '561 patent discloses three basic and novel properties of the invention, each of which is directed to the properties of the *perfusion*: (1) perfusions prepared from the stock solutions can contain 1 mg/ml or less of docetaxel, (2) the perfusion is physically stable (*i.e.*, no precipitation within approximately eight hours), and (3) the perfusion can be administered without the "anaphylactic shock phenomena which were observed with these solutions of the prior art . . . ." (Tr. at 526:10-527:11 (Kaler); *see also* JTX 3 at 2:37-51.) Defendants improperly focus on the effect that their extra excipients purportedly have on their *stock solutions*, which (based on the intrinsic evidence) is completely irrelevant to the basic and novel properties of the invention.

118.

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119.

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120.

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121. Defendants' reliance on statements in the '561 patent file history purporting to distinguish the invention from "three-solvent systems," such as Tarr, misrepresents the file history. Applicants distinguished the invention from Tarr because it, like both accused products, uses polysorbate as the *sole surfactant*. (JTX 4 at SA00013023, 13049.) In allowing the claims, the Examiner confirmed that only "*carriers* [*i.e.* surfactants] having similar characteristics as pluronic L64 are excluded from the claims". (*Id.* at SA00013141 (emphasis added).)

B. Claims 2 and 10 Are Not Obvious

122. Defendants assert that Claims 2 and 10 are rendered obvious by the '470 patent in

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combination with various references such as G-V, etoposide, and the "surfactant swap art". Because Claims 2 and 10, drawn to compositions "consisting essentially of" polysorbate and ethanol, are narrower than the open Claim 5, these arguments fail for the reasons already discussed in connection with Claim 5. (*See supra* ¶¶ 54-57, 62-65, 69-82, 84-101; *see also supra* ¶¶ 102-111 ("without anaphylactic or alcohol intoxication manifestations. . ." is definite and enabled).) In addition, any suggestion that the etoposide formulation renders Claims 2 and 10 obvious is refuted by the testimony of Hospira's own formulator that benzyl alcohol, one of the ingredients in etoposide, is unsuitable for taxanes. (*See supra* ¶ 73.)

C. Claims 2 and 10 Are Not Indefinite

123. Defendants also contend that the phrase "used to form" in Claims 2 and 10 is indefinite because composition claims cannot permissibly contain a method step, such as "used to form" is alleged to be. But Claims 2 and 10 merely define the two types of compositions discussed throughout the patent and claimed as the inventions covered by the '561 patent—stock solutions and perfusions. A composition that is *used to form* an injectable solution is a stock solution—a term the Court construed to mean a concentrated solution. (Tr. 522:7-17 (Kaler).) A composition that *forms* an injectable solution is a perfusion. (*Id.*)

IV. CLAIM 7 OF THE '512 PATENT IS INFRINGED AND NOT INVALID

A. Both Defendants Infringe Claim 7

124. Claim 7 of the '512 patent essentially has three elements: (1) a "composition" (which can be either a stock solution or a perfusion, *see* D.I. 44 at 1); (2) with docetaxel dissolved in polysorbate; and (3) essentially free or free of ethanol. (JTX 1 at cl. 7; Tr. 658:5-659:10 (Myerson).) It is undisputed that both Defendants' perfusions contain docetaxel dissolved in polysorbate. (UF ¶¶ 56-57, 64; Tr. 659:11-660:10 (Myerson).) The only area of dispute concerns the requirement that a perfusion be "essentially free or free of ethanol".

125. This Court construed "essentially free or free of ethanol" to mean, for a perfusion, "the same amount of ethanol as a stock solution with no more than 5% ethanol by volume". (D.I. 347 at 2.) To apply this construction, one would logically look to a stock solution which would define the maximum level at which a stock solution (and therefore, a perfusion with the same amount of ethanol) could be essentially free of ethanol. Defendants have identified such a stock solution as part of their *invalidity* analysis, which has 5% by volume ethanol and 2 mg/ml of docetaxel. (Tr. 1178:15-1179:1 (Williams).)

126. Once this stock solution is identified, "it follows, by simple mathematics . . . what essentially free will mean in any perfusion." (Tr. 662:5-7 (Myerson).)

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At 1 mg/ml, the maximum perfusion concentration according to the Patents-in-Suit, (JTX 1 at 2:31), the percentage would be 2.5%.[21]

127. In light of its own invalidity contentions, Hospira does not—and cannot—dispute that a perfusion which is "essentially free or free of ethanol" can contain *more* ethanol than Hospira's perfusion.

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(*E.g.*, D.I. 362 at 3-4.)

This approach is legally improper. *See, e.g., Vanguard Prods. Corp. v. Parker Hannifin Corp.*, 234 F.3d 1370, 1372 (Fed. Cir. 2000) (*composition* claims cannot be limited according to the *process* by which they are made).

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REDACTED

128. Dr. Myrdal also suggested that, under Plaintiffs' analysis, the definition of "essentially free or free of ethanol" would change in future cases depending on the indicated docetaxel concentrations of a future accused product. (Tr. 877:6-882:12.) But a 2 mg/ml stock solution with 5% ethanol is the proper yardstick for the ethanol upper limit, because it is the least concentrated stock solution (given that the Patents-in-Suit disclose a maximum perfusion concentration of 1 mg/ml, *see* JTX 1 at 2:31.) The analysis would be consistent because the *5% ethanol stock solution* would be a constant.[22] (Tr. 668:25-670:15, 670:21-673:10 (Myerson).)

129.

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130.

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But the preferred embodiments set forth in the '512 patent itself consistently teach that a composition according to the invention can be created by first "dissolving" the docetaxel in *ethanol*, and only *then* adding the surfactant to the mixture. (*E.g.*, JTX 1 at 4:33-34 (Examples 1-7: "Taxotere (32 g) is dissolved in absolute ethanol (340 ml) and Polysorbate 80 (830 g) is *then* added" (emphasis added).) Thus, Apotex's reading of "dissolved" cannot be correct because it would exclude nearly all of the preferred embodiments of the Patents-in-Suit. *See, e.g., Anchor Wall Sys., Inc. v. Rockwood Retaining Walls, Inc.*, 340 F.3d 1298, 1308 (Fed. Cir. 2003) ("it is axiomatic that a

[22] Hospira also asserts that Dr. Myerson "use[d] Hospira's accused product to define his standard for what is 'essentially free' of ethanol, and then applies that standard back again to Hospira's product." (D.I. 362 at 4.) That is wrong—the standard is the *5% ethanol stock solution.*

claim construction that excludes a preferred embodiment . . . 'is rarely, if ever correct and would require highly persuasive evidentiary support.'" (internal quotation omitted)). Rather, the plain and ordinary meaning of dissolved is that the docetaxel is in a solution with polysorbate.

B. Claim 7 Is Not Obvious

131. Defendants assert that Claim 7 is rendered obvious by the '470 patent (in combination with either G-V or the "surfactant swap art"), and Tarr. These arguments fail in large part for the reasons already discussed in connection with Claims 2, 5, and 10. (*See supra* ¶¶ 54-65, 69-82, 84-101.) In addition, Defendants assert that Tarr (JTX 16) renders Claim 7 obvious by showing low ethanol. This is incorrect. Rather, the formulation with the "greatest solubilizing . . . properties" according to Tarr (*id.* at 32) had 30% ethanol, far above the 5% limit for stock solutions. A person of ordinary skill in the art would not have been led to a formulation with less than 5% ethanol by an article disclosing that 30% was "needed in order to increase the solubility of pluronic L64 in water and enable its rapid solubilization." (*Id.*) This is consistent with the belief at the time of the invention that ethanol was necessary to solubilize taxanes in polysorbate, a misimpression stemming from slow precipitation kinetics of taxanes in pure surfactant, a belief that would teach away from the claimed invention. (*See supra* ¶ 15.)

132. As for whether an "essentially free of ethanol" perfusion is disclosed, Tarr discloses that the concentration of the paclitaxel formulation was 5 mg/ml with 30% ethanol. (*Id.*) Diluting to the maximum perfusion concentration, 1 mg/ml, would leave a concentration of 6% ethanol, well above the 2.5% benchmark established above. (*See supra* ¶ 126.)

C. The '512 Patent Is Not Invalid for Double Patenting

133. Apotex asserts that both asserted claims of the '512 patent are invalid for obviousness-type double patenting over Claims 1 and 44 of U.S. Patent No. 5,698,582, another *Orange Book* patent scheduled to expire on the same day as the '512 patent, July 3, 2012. This argument is

obviated by a terminal disclaimer, (JTX 286 at FIN01-000394-397), transmitted to the PTO on November 8, 2007. (*Id.* at FIN01-000398; *see also* 1348 *Official Gazette* 420 (Nov. 24, 2009), *available at* http://www.uspto.gov/web/offices/com/sol/og/2009/week47/TOC.htm#ref16.)

V. CLAIM 33 OF THE '512 PATENT IS INFRINGED AND NOT INVALID

A. Both Defendants Infringe Claim 33

134. Claim 33 has three elements: (1) a "stock solution" (construed to mean a "concentrated solution, *see* D.I. 347); (2) with 10 mg/mL to 200 mg/mL of docetaxel; (3) dissolved in polysorbate. (JTX 1, cl. 33; Tr. 675:21-676:10 (Myerson).)

135. Hospira put forward no non-infringement evidence with respect to Claim 33. Accordingly, Hospira's NDA product directly infringes Claim 33. (*See also* D.I. 364 at 5.)

136.

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137. Apotex's only non-infringement defense is to assert that the "dissolved in a surfactant" limitation of Claim 33 is not met because **REDACTED** This argument, as noted above, is contrary to the intrinsic evidence. (*See supra* ¶ 130.)

B. Claim 33 Is Not Invalid

138. Defendants assert that Claim 33 is anticipated by G-V, and rendered obvious by the '470 patent in combination with G-V or the "surfactant swap art." These arguments fail for the reasons already discussed. (*See supra* ¶¶ 54-57, 62-65, 82, 84-101.) Additional invalidity arguments specific to Claim 33 are discussed further below.

1. G-V Does Not Anticipate Claim 33

139. In addition to the reasons stated above (*see supra* ¶¶ 62-65, 79), G-V does not anticipate Claim 33 because the concentrations of docetaxel in the solutions disclosed, to the extent any are, are far below the concentrations required by Claim 33 (between 10 mg/ml and 200 mg/ml docetaxel). (Tr. 958:8-959:3 (Myrdal).) Table III of the article reports data on docetaxel's potency in inhibiting P388 leukemic cell growth. The concentration of docetaxel reported is 0.13 μg/mL (*see* JTX 93, tbl. III note a), or 0.00013 mg/ml. (Tr. 1460:21-1461:21 (Park).)

2. Claim 33's Docetaxel Concentration Range Is Enabled

140. The '512 patent *specifically* teaches how to make a stock solution of 200 mg/mL (as required by Claim 33) simply by dissolving 100 mg/mL in a 50:50 polysorbate/ethanol solution, and then evaporating all of the ethanol (which of course causes the docetaxel concentration to double to 200 mg/mL). (JTX 1 at 3:8-11.) And, Hospira itself created a stock solution with ethanol, polysorbate 80, and 217 mg/mL docetaxel. (Tr. 815:5-819:12 (Liu).)

VI. THE PATENTS-IN-SUIT ARE ENFORCEABLE

141. An inequitable conduct claim requires that two distinct elements be demonstrated by clear and convincing evidence: (1) that an individual associated with the filing or prosecution of a patent application made an affirmative misrepresentation of a material fact or failed to disclose material information; (2) with a specific intent to deceive the PTO. *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1365 (Fed. Cir. 2008).

142. With respect to the intent element, "the alleged conduct must not amount merely to the improper performance of, or omission of, an act one ought to have performed. Rather, clear and convincing evidence must prove that an applicant had the specific intent to accomplish an act that the applicant ought not to have performed, *viz.*, misleading or deceiving the PTO. In a case involving nondisclosure of information, clear and convincing evidence must show that the applicant made a deliberate decision to withhold a known material reference." *Mollins PLC v.*

Textron, Inc., 48 F.3d 1172, 1181 (Fed. Cir. 1995).

143. A reference is not "material" if it is cumulative to other references already before the Examiner. *See Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1337 (Fed. Cir. 2008).

A. M. Fabre Did Not Wrongly or Intentionally Fail To Disclose G-V

144. Defendants allege that M. Fabre was aware of the March 1991 published version of the G-V prior art reference, but chose not to disclose it to the PTO. Defendants claim that G-V is material to patentability solely based on one sentence in the article, which mentions the comparative solubility of docetaxel (and two other taxanes) in polysorbate and ethanol. This sentence is not material to either Patent-in-Suit for the reasons stated above in the invalidity context. (*See supra* ¶¶ 62-65, 79.) But more to the point, Defendants' inequitable conduct allegation was *conclusively disproved* at trial by M. Fabre's testimony concerning a March 1990 *draft* of G-V that did not contain the very sentence upon which Defendants rely. (PTX 724/724-T at SA00880726.) M. Fabre testified that he reviewed this draft in March 1990, (Tr. 500:19-503:15), a month before the article was received by the publisher (*see* JTX 93 at 992). He did not know (until this litigation) that the draft was later altered to include the sentence mentioning polysorbate (Tr. 504:14-18), and had no reason to recheck the final version because he assumed that it was the same version he reviewed before it went to the publisher (Tr. 504:3-13).

B. M. Fabre Did Not Wrongly or Intentionally Fail To Disclose Etoposide

145. Defendants accuse M. Fabre of inequitable conduct with respect to the etoposide prior art formulation, relying largely on one sentence of a December 1988 internal memo mentioning the Sandoz experience with etoposide. (JTX 162 at SA00879661.) Defendants are wrong.

146. *First*, a year before the filing of the French application, in 1990, the inventors tested docetaxel with the etoposide formulation and variations thereof, and the tests were a failure because docetaxel did not have adequate physical stability in the etoposide formulation. (*See*

supra ¶ 12.) M. Fabre did not believe that he was required to inform the PTO of his numerous failed formulation attempts before he arrived at his invention. (Tr. 499:20-500:7.) Not only do these failed tests underscore the immateriality of etoposide, but the fact that the inventors believed the formulation to have failed with a taxane negates any inference of intent to deceive.

147. *Second*, M. Fabre testified that, at the time, he considered the etoposide formulation different than his invention due to the fact that those formulations also contained additional excipients such as PEG. (Tr. 448:23-449:13, 450:18-22.) This view further negates any inference of his intent to withhold material information.

148. *Third*, there was information concerning the relative toxicology profiles of Cremophor and polysorbate known to the inventors in 1988 suggesting that polysorbate 80 would *not* be an improvement over Cremophor. (Tr. 405:15-410:3 (Fabre); JTX 161 at SA00879677 ("recent information is leading to the conclusion that . . . TWEEN could present the same type of anaphylactic reaction as Cremophor").)

149. *Fourth*, even leaving aside Defendants' failure to prove intent, etoposide is not relevant to taxane formulations and accordingly were not material to patentability. Because it is not a taxane, etoposide did not show the benefit of using polysorbate 80 *with a taxane*. (Tr. 1467:9-1471:4 (Park).) Indeed, the etoposide formulation was known in the art at least by 1981, well before Taxol (ATX 538 at 117-19; *see also* JTX 102 at 959), yet Taxol was formulated in Cremophor anyway. This is because, as already discussed, it was universally believed that there was no usable alternative to Cremophor for a taxane. (*See supra* ¶¶ 86-92.)

150. At most, etoposide is cumulative to the Tarr reference, which was before the Examiner. The Tarr reference discloses a paclitaxel formulation with 10% polysorbate, higher than the 8% polysorbate concentration in etoposide. (*See supra* ¶¶ 58, 74.)

C. M. Fabre Did Not Mislead With Respect to Anaphylactic Shock

151. Defendants also contend that M. Fabre misled the Patent Office when he stated that, in the (translated) words of the French application filed in July 1991 "[t]he anaphylactic shock phenomena which were observed with the solutions of the prior art are not observed with these solutions." (JTX 12-T at 5:4-5.) M. Fabre testified that his basis for these statements was that anaphylaxis was avoided by his invention compared to Taxol, (*id.* at JA0093, JA0095) was the reports he received in his capacity as Project Leader regarding the success of the Phase I clinical trials, which had begun in June 1990. (Tr. 429:24-430:10, 434:10-437:14.) In particular, by July 3, 1991, M. Fabre had received reports showing that, not only had the target dose of 100 mg/m^2 been attained with *no* anaphylactic shock incidents observed to date, but that the *in vivo* activity of docetaxel had been confirmed. (Tr. 426:9-429:23.) Five days after this confirmation of success, he filed his patent application. (Tr. 429:24-430:7.) Defendants have adduced *no* evidence contradicting this testimony, which establishes a good-faith basis for the representations in the application. Even if Defendants succeed in redefining "anaphylactic manifestations" to encompass even fluid retention and rashes (which they should not, *see supra* ¶ 47), that would still not establish M. Fabre's *intent* to mislead the PTO on this issue.

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